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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,773	JUNGHANS, RICHARD P.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group II, claims 2 and 5-7 in part, in the reply filed on 5/9/05 is acknowledged. Upon further consideration the restriction between Groups I-IV is vacated. It is noted that claims 8-9 have been amended and would be restricted as four separate groups each method using one of the separate chimeric molecules of Groups I-IV in the original restriction. Therefore, the restriction between the method Groups is maintained.

The requirement is still deemed proper and is therefore made **FINAL**.

2. Claims 8-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/9/05.

3. Claims 1-7 are under examination.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

> The Oath/Declaration filed with the application does not appear to be a true Oath/Declaration and is missing essentially all of the requirements as indicated below:

The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602.

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

It does not state that the person making the oath or declaration acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56.

The clause regarding "willful false statements ..." required by 37 CFR 1.68 has been omitted.

It does not identify the citizenship of each inventor.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Specification

5. The abstract of the disclosure is objected to because the specification contains one abstract not on a separate page (see page 11) and a separate page with the abstract (see amendment filed 3/28/02) Applicant is requested to cancel the abstract on page 11. Correction is required. See MPEP § 608.01(b).

6. The disclosure is objected to because of the following informalities: The amendment filed 1/25/05 and 5/9/05 submits to amend the Figures but it appears that the only amendment is to the Brief description of the Drawings. In addition, it appears that Figure 3 is a diagram of a vector and has no sequences disclosed and it is not clear what the addition of SEQ ID NO1 and 2 have to do with the figure. Also the amendment added "SEQ.#3" for example and the standard convention is "SEQ ID NO:3" for

example. In addition, the identifiers "(presently amended)" are not needed and applicant should follow the correct method of amendment which are in MPEP 714.

Appropriate correction is required.

Claim Objections

7. Claims 2 and 5-7are objected to because of the following informalities:

a. Claim 2 contains a typographical error in the term "hchain" I should be "chain".

b. Claims 5-7 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim needs to be recited as indicated in MPEP § 608.01(n). Accordingly, claims 5-7 will be examined as depending only on claim 1 or 2 or 3 or 4.

c. Claims 5-7 are objected to for failing to further limit claims 1-4. Claim 5 recites a broadening of claims 1-4 by reciting other cell types or different hinges or no hinge where claims 1-4 requires a zeta signaling chain of a T cell receptor and a specific hinge. Claim 6 does not further limit because claims 1-4 requires the CDRs in specific figures but claim 6 only requires at least one. Claim 7 does not further limit claims 1-4 because the claim requires a different DNA or protein sequence for the antibody binding domain and claims 1-4 requires a specific sequence.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-4 are indefinite for reciting the term "gene" because the exact meaning of the term is not clear. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as Athe segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons). From the teachings of the specification, however, the nucleic acid sequences appear limited to the specific coding regions, and do not include expression control elements that fall under the definition of a gene. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

b. Claim 5 is indefinite for reciting "other cell types" because it is not clear what the other cell types are or what signaling chains are contemplated.

c. Claim 5 is indefinite for reciting "a different hinge molecule or no hinge molecule is substituted" because it is not clear if the phrase means substitution of the hinge with a different hinge or removing the hinge all together.

d. Claim 6 is indefinite for reciting the second sentence because it is not clear if this is a comment or a limitation in the claim and in addition a claim can not have two sentences. In addition, claim 6 is indefinite for reciting that at least one of the CDRs of the heavy chain and at least one CDR of the light chain are preserved in a form (e.g. sFv or Fab) because it is not clear again if the "e.g." is a limitation or not and it is unclear how a CDR can be in a form of a sFv or Fab. CDRs are in antibody fragments of sFv and Fabs but they are not in a "form" of such.

e. Claim 7 is indefinite for reciting "modified in DNA or protein sequence but which retains the specificity and action of these molecules" because it is unclear which part of the molecules are modified. Is only the binding domain modified or is only the T cell receptor signaling chain, or is the hinge or are all parts modified? In addition it is unclear what "specificity or action" of the molecules are contemplated. Is it binding to the antigen, T cell signaling?

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4 recites the term "gene". It appears that the specification only discloses a leader and DNA sequences for the VL and VH chains of an immunoglobulin (see brief description of the drawings). There is no description for introns, exons, control elements, etc. that are encompassed in the definition of a "gene". Therefore, one skill in the art would conclude that applicant was not in possession of the claimed invention at the time the application was filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

12. Claims 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric molecule comprising the antigen binding domain of the specific single-chin Fv molecules with the amino acid sequence of the specific antibodies with all 6 CDRs of the specific antibodies and the zeta signaling chain of the T cell receptor or other signaling domains for T cell activation and a CD8alpha hinge with or without the cysteines mutated, does not reasonably provide enablement for a chimeric molecule with just any signaling chains of just any cell type or without the hinge or only one CDR from the heavy and light chains of the specified antibodies or just any modified protein sequences of such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any molecule with signaling chains from any cell and a molecule without the hinge and molecules which do not contain a full set of CDRs for the single chain binding molecule and molecules with protein sequences modified at any positions including the CDRs. The specification discloses single chain molecules of

3D8, MB3.6, 4D4, 3E11 and zeta signaling chain of a T cell and T cell receptor molecules and all have the CD8alpha hinge (see page 6 and Figures). The specification does not enable any molecules that do not have a hinge or that are modified in protein sequences in the CDRs or scFV that have only one CDR of a heavy and light chain.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass all modifications to the amino acid sequence because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).f

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

The claims encompass scFv with only one CDR of each chain either defined or only one CDR from each chain or modifications in the CDRs. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, it is unlikely that scFv's as defined by the claims which may contain less than the full complement of CDRs from the heavy and

light chain variable regions or comprise any amino acid substitution in the hypervariable region of the heavy chain and light chain variable domain, specifically the CDRs, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claim 5 is broadly drawn to a molecule with no hinge (see 112 second above). As evidenced from Moritz et al (Gene Therapy 2:539-546, 1995) a spacer region of a hinge is required for ligand binding and signaling (see entire document). Therefore, one skill in the art would conclude that molecules that lack the spacer, which is encompassed by the claim, would not function.

Therefore, in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of molecules encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 2, 3, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moritz et al (Gene Therapy 2:539-546, 1995), and further in view of Fitzer-Attas et al (The Journal of Immunology 160:145-154, 1998) and Murphy et al (US Patent 6150508, filed 3/18/98) and Robinson et al (US Patent 5,618,920, issued 4/97).

The claims recite a chimeric molecule comprised of the PSMA binding domain of the 3D8 or the 4D4 antibody as a scFV with sequences of Figure 4D and E or 4F and G and a linker and the zeta signaling chain of the T cell receptor and a CD8alpha hinge with cysteines mutated and further claimed is other signaling chains of other cell types and different hinges and different linkers and different DNA sequences.

Moritz et al teach a single chain protein with a linker and the zeta chain of the T cell receptor and a CD8alpha hinge and the construct is used to target T cells to tumor cells and the scFV binds the tumor antigen ErbB-2 (see abstract and Figure 1). Moritz et al does not teach other signaling chains of other molecules or the 3D8 or 4D4 binding

domain or a mutated CD8alpha hinge. these deficiencies are made up for in the teachings of Fitzer-Attas et al, Murphy et al, and Robinson et al.

Fitzer-Attas et al teach scFv-DCD8alpha mutated hinge-signaling domains from other cells for T cell activation (see entire document, especially bottom left of page 146). The reference demonstrates the use of a mutated hinge and other signaling domains as well as other sequences of proteins was known in the art.

Murphy et al teach the 3D8 and 4D4 antibody and hybridoma (see Table 2 and Part 9 for deposits)

Robinson et al teach obtaining the sequences of the heavy and light chains from cells, specifically hybridomas (see column 12-22).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric molecule comprising the 3D8 or 4D4 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Moritz et al, Fitzer-Attas et al, Murphy et al, and Robinson et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric molecule comprising the 3D8 or 4D4 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Moritz et al, Fitzer-Attas et al, Murphy et al, and Robinson et al because Moritz et al uses a ScFv molecule that binds a tumor target fused to a CD8 hinge and the zeta chain of a T cell receptor to target tumors and it would have been obvious to substitute the antigen binding domain of the

3D8 or the 4D4 antibody because Murphy et al teach the antibody binds the tumor antigen PSMA and targets tumor cells. It would have been obvious that Moritz et al had the hybridoma because this cell is used to produce the antibody. It would have been obvious to obtain the DNA and protein sequence of the 3D8 and 4D4 antibody and obtain the sequences in Figures 4D-E and 4F-G because Robinson et al teach methods of obtaining the sequences from the hybridoma and at the time of the claimed invention this was routinely done. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the claimed invention and substituted the CD8alpha hinge with another hinge or one with a mutated cysteine because Fitzer-Attas et al specifically teach doing so and the reasons why a mutated hinge is desirable. In addition, it would be obvious that altering the signaling domain from the zeta chain to that of Fitzer-Attas et al would alter the DNA and amino acid sequence and still have the same function of targeting a tumor and T cell activation. In addition, it would have been obvious to use the claimed linker or other linkers because the use of a linker in the construction of a scFv is routine and the prior art teaches many can be used for production of scFvs.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moritz et al (Gene Therapy 2:539-546, 1995), and further in view of Fitzer-Attas et al

(The Journal of Immunology 160:145-154, 1998) and Cheresh et al (PNAS 82:5155-59, 1985) and Robinson et al (US Patent 5,618,920, issued 4/97).

The claims recite a chimeric molecule comprised of the GD3 binding domain of the MB3.6 antibody as a scFV with sequences of Figure 4A-C and a linker and the zeta signaling chain of the T cell receptor and a CD8alpha hinge with cysteines mutated and further claimed is other signaling chains of other cell types and different hinges and different linkers and different DNA sequences.

Moritz et al teach a single chain protein with a linker and the zeta chain of the T cell receptor and a CD8alpha hinge and the construct is used to target T cells to tumor cells and the scFV binds the tumor antigen ErbB-2 (see abstract and Figure 1). Moritz et al does not teach other signaling chains of other molecules or the MB3.6 binding domain or a mutated CD8alpha hinge. These deficiencies are made up for in the teachings of Fitzer-Attas et al, Cheresh et al, and Robinson et al.

Fitzer-Attas et al teach scFv-DCD8alpha mutated hinge-signaling domains from other cells for T cell activation (see entire document, especially bottom left of page 146). The reference demonstrates the use of a mutated hinge and other signaling domains as well as other sequences of proteins was known in the art.

Cheresh et al teach the MB3.6 antibody and hybridoma (see Material and Methods)

Robinson et al teach obtaining the sequences of the heavy and light chains from cells, specifically hybridomas (see column 12-22).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric molecule comprising the MB3.6 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Moritz et al, Fitzer-Attas et al, Cheresh et al, and Robinson et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric molecule comprising the MB3.6 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Moritz et al, Fitzer-Attas et al, Cheresh et al, and Robinson et al because Moritz et al uses a ScFv molecule that binds a tumor target fused to a CD8 hinge and the zeta chain of a T cell receptor to target tumors and it would have been obvious to substitute the antigen binding domain of the MB3.6 antibody because Cheresh et al teach the antibody binds the tumor antigen GD3 and targets tumor cells. It would have been obvious that Moritz et al had the hybridoma because this cell is used to produce the antibody. It would have been obvious to obtain the DNA and protein sequence of the MB3.6 antibody and obtain the sequences in Figures 4A-C because Robinson et al teach methods of obtaining the sequences from the hybridoma and at the time of the claimed invention this was routinely done. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the claimed invention and substituted the CD8alpha hinge with another hinge or one with a mutated cysteine because Fitzer-Attas et al specifically teach doing so and the reasons why a mutated

hinge is desirable. In addition, it would be obvious that altering the signaling domain from the zeta chain to that of Fitzer-Attas et al would alter the DNA and amino acid sequence and still have the same function of targeting a tumor and T cell activation. In addition, it would have been obvious to use the claimed linker or other linkers because the use of a linker in the construction of a scFv is routine and the prior art teaches many can be used for production of scFvs.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moritz et al (Gene Therapy 2:539-546, 1995), and further in view of Fitzer-Attas et al (The Journal of Immunology 160:145-154, 1998) and Murphy et al (The Journal of Urology 160:2396-2401, 12/98) and Robinson et al (US Patent 5,618,920, issued 4/97).

The claims recite a chimeric molecule comprised of the PSMA binding domain of the 3E11 antibody as a scFV with sequences of Figure 4H-I and a linker and the zeta signaling chain of the T cell receptor and a CD8alpha hinge with cysteines mutated and further claimed is other signaling chains of other cell types and different hinges and different linkers and different DNA sequences.

Moritz et al teach a single chain protein with a linker and the zeta chain of the T cell receptor and a CD8alpha hinge and the construct is used to target T cells to tumor cells and the scFV binds the tumor antigen ErbB-2 (see abstract and Figure 1). Moritz et al does not teach other signaling chains of other molecules or the 3E11 binding

domain or a mutated CD8alpha hinge. these deficiencies are made up for in the teachings of Fitzer-Attas et al, Murphy et al, and Robinson et al.

Fitzer-Attas et al teach scFv-DCD8alpha mutated hinge-signaling domains from other cells for T cell activation (see entire document, especially bottom left of page 146). The reference demonstrates the use of a mutated hinge and other signaling domains as well as other sequences of proteins was known in the art.

Murphy et al teach the 3E11 antibody and hybridoma (see Table results and Figure 1)

Robinson et al teach obtaining the sequences of the heavy and light chains from cells, specifically hybridomas (see column 12-22).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric molecule comprising the 3E11 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Moritz et al, Fitzer-Attas et al, Murphy et al, and Robinson et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric molecule comprising the 3E11 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Moritz et al, Fitzer-Attas et al, Murphy et al, and Robinson et al because Moritz et al uses a ScFv molecule that binds a tumor target fused to a CD8 hinge and the zeta chain of a T cell receptor to target tumors and it would have been obvious to substitute the antigen binding domain of the

3E11 antibody because Murphy et al teach the antibody binds the tumor antigen PSMA and targets tumor cells. It would have been obvious that Moritz et al had the hybridoma because this cell is used to produce the antibody. It would have been obvious to obtain the DNA and protein sequence of the 3E11 antibody and obtain the sequences in Figures 4H-I because Robinson et al teach methods of obtaining the sequences from the hybridoma and at the time of the claimed invention this was routinely done. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the claimed invention and substituted the CD8alpha hinge with another hinge or one with a mutated cysteine because Fitzer-Attas et al specifically teach doing so and the reasons why a mutated hinge is desirable. In addition, it would be obvious that altering the signaling domain from the zeta chain to that of Fitzer-Attas et al would alter the DNA and amino acid sequence and still have the same function of targeting a tumor and T cell activation. In addition, it would have been obvious to use the claimed linker or other linkers because the use of a linker in the construction of a scFv is routine and the prior art teaches many can be used for production of scFvs.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

17. Claims 1, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan et al (Clinical Cancer Res 5:3928-3941, 12/99) and further in view of Fitzer-Attas

et al (The Journal of Immunology 160:145-154, 1998) and Cheresh et al (PNAS 82:5155-59, 1985).

The claims have been described supra.

Nolan et al teach a chimeric molecule comprised of the CEA binding domain of the humanized MN14 antibody and a linker and the zeta signaling chain of the T cell receptor and a CD8alpha hinge with cysteines mutated and the sequences obtained from the hybridoma (see entire document). Nolan et al does not teach other signaling chains of other molecules or the MB3.6 antibody. These deficiencies are made up for in the teachings of Fitzer-Attas et al and Cheresh et al.

Fitzer-Attas et al teach scFv-DCD8alpha mutated hinge-signaling domains from other cells for T cell activation (see entire document, especially bottom left of page 146). The reference demonstrates the use of a mutated hinge and other signaling domains as well as other sequences of proteins was known in the art.

Cheresh et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric molecule comprising the MB3.6 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Nolan et al and Fitzer-Attas et al and Cheresh et al,

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric molecule comprising the MB3.6 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a

hinge of CD8alpha with mutated cysteines in view of Nolan et al and Fitzer-Attas et al and Cheresh et al, because Nolan et al teaches a hMN14-TCR molecule wherein the molecule binds a cancer antigen and it would have been obvious to substitute another signaling chain of a T cell because Fitzer-Attas teaches targeting tumors with scfv and t cell receptor constructs using other signaling chains (see page 146) and it would have been obvious to substitute the antigen binding region of the MB3.6 antibody because Cheresh et al teach the antibody binds to a cancer antigen. In addition, it would be obvious that altering the signaling domain from the zeta chain to that of Fitzer-Attas et al would alter the DNA and amino acid sequence and still have the same function of targeting a tumor and T cell activation. In addition, it would have been obvious to use the claimed linker or other linkers because the use of a linker in the construction of a scFv is routine and the prior art teaches many can be used for production of scFvs. In addition, it would have been obvious to modify the DNA and encode the same protein because of the degeneracy in the DNA code.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 2, 3, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan et al (Clinical Cancer Res 5:3928-3941, 12/99) and further in view of Fitzer-Attas et al (The Journal of Immunology 160:145-154, 1998) and Murphy et al (US Patent 6150508, Filed 3/98).

The claims have been described supra.

Nolan et al teach a chimeric molecule comprised of the CEA binding domain of the humanized MN14 antibody and a linker and the zeta signaling chain of the T cell receptor and a CD8alpha hinge with cysteines mutated and the sequences obtained from the hybridoma (see entire document). Nolan et al does not teach other signaling chains of other molecules or the 3D8 or 4D4 antibody. These deficiencies are made up for in the teachings of Fitzer-Attas et al and Murphy et al.

Fitzer-Attas et al teach scFv-DCD8alpha mutated hinge-signaling domains from other cells for T cell activation (see entire document, especially bottom left of page 146). The reference demonstrates the use of a mutated hinge and other signaling domains as well as other sequences of proteins was known in the art.

Murphy et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric molecule comprising the 3D8 or 4D4 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Nolan et al and Fitzer-Attas et al and Murphy et al,

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric molecule comprising the 3D8 or 4D4 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Nolan et al and Fitzer-Attas et al and Murphy et al, because Nolan et al teaches a hMN14-TCR molecule wherein the molecule binds a cancer antigen and it would have been obvious to substitute another

signaling chain of a T cell because Fitzer-Attas teaches targeting tumors with scfv and t cell receptor constructs using other signaling chains (see page 146) and it would have been obvious to substitute the antigen binding region of the 3D8 or 4D4 antibody because Murphy et al teach the antibody binds to a cancer antigen. In addition, it would be obvious that altering the signaling domain from the zeta chain to that of Fitzer-Attas et al would alter the DNA and amino acid sequence and still have the same function of targeting a tumor and T cell activation. In addition, it would have been obvious to use the claimed linker or other linkers because the use of a linker in the construction of a scFv is routine and the prior art teaches many can be used for production of scFvs. In addition, it would have been obvious to modify the DNA and encode the same protein because of the degeneracy in the DNA code.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. Claims 4, 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nolan et al (Clinical Cancer Res 5:3928-3941, 12/99) and further in view of Fitzer-Attas et al (The Journal of Immunology 160:145-154, 1998) and Murphy et al (The Journal of Urology 160:2396-2401, 1998).

The claims have been described supra.

Nolan et al teach a chimeric molecule comprised of the CEA binding domain of the humanized MN14 antibody and a linker and the zeta signaling chain of the T cell receptor and a CD8alpha hinge with cysteines mutated and the sequences obtained

from the hybridoma (see entire document). Nolan et al does not teach other signaling chains of other molecules or the 3D8 or 4D4 antibody. These deficiencies are made up for in the teachings of Fitzer-Attas et al and Murphy et al.

Fitzer-Attas et al teach scFv-DCD8alpha mutated hinge-signaling domains from other cells for T cell activation (see entire document, especially bottom left of page 146). The reference demonstrates the use of a mutated hinge and other signaling domains as well as other sequences of proteins was known in the art.

Murphy et al has been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric molecule comprising the 3E11 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Nolan et al and Fitzer-Attas et al and Murphy et al,

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric molecule comprising the 3E11 scFv and a zeta signaling chain or a CD4 or CD8 signaling domain and a hinge of CD8alpha with mutated cysteines in view of Nolan et al and Fitzer-Attas et al and Murphy et al, because Nolan et al teaches a hMN14-TCR molecule wherein the molecule binds a cancer antigen and it would have been obvious to substitute another signaling chain of a T cell because Fitzer-Attas teaches targeting tumors with scfv and t cell receptor constructs using other signaling chains (see page 146) and it would have been obvious to substitute the antigen binding region of the 3E11 antibody because

Murphy et al teach the antibody binds to a cancer antigen. In addition, it would be obvious that altering the signaling domain from the zeta chain to that of Fitzer-Attas et al would alter the DNA and amino acid sequence and still have the same function of targeting a tumor and T cell activation. In addition, it would have been obvious to use the claimed linker or other linkers because the use of a linker in the construction of a scFv is routine and the prior art teaches many can be used for production of scFvs. In addition, it would have been obvious to modify the DNA and encode the same protein because of the degeneracy in the DNA code.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 10/006771 in view of Murphy et al (US Patent 6150508) and Cheresh et al (PNAS 82:5155-59, 1985) and Murphy et al (The Journal of Urology 160:2396-2401, 1998).

The claims in the instant application are drawn to a chimeric molecule comprising Mb3.6, 3D8, 4D4, or 3E11 hMN14 antibody as a single chain and the zeta signaling chain of the T cell receptor and a CD8 alpha hinge in which the cysteine residues have been mutated and further claimed is other signaling chins, and modified DNA that retains specificity. The claims in the 10/006771 application are drawn to a chimeric molecule comprising the hMN14 antibody as a single chain and the zeta signaling chain of the T cell receptor and a CD8 alpha hinge in which the cysteine residues have been mutated and further claimed is other signaling chins, and modified DNA that retains specificity.

It would have been obvious to substitute the GD3 or PSMA binding domain of the claimed antibody with of the CEA binding domain in the 10/006771 application because the antibody in the claims in application 10/006771 bind cancer antigens and the antibody of Murphy et al and Cheresh et al also binds a cancer antigen. It would have been obvious to target the GD3 or PSMA antigen because Cheresh and Murphy et al all teach the antibodys binds cancers. The molecules in the instant application are obvious variants of that in the 10/006771 application because all of the molecules are used to treat cancers and the only difference is the targeting antibody and it would have been

obvious to use any antibody that targets a cancer antigen. Therefore, the claims are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:00 am to 3:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

24. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER